

INTERNATIONAL SEARCH REPORT

International Application No

/GB2004/001453

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/26 C12N9/02 C12N15/00 C12Q1/68 C07K16/00
A61K48/00 A61K38/00 C12N15/86 C12N5/10 G01N33/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, Sequence Search, PAJ, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/79468 A (INCYTE GENOMICS INC ; PATTERSON CHANDRA (US); TRIBOULEY CATHERINE M (U) 25 October 2001 (2001-10-25) the whole document in particular: sequences 6,16 page 29, line 10 - line 27 page 27, line 32 - page 28, line 4 page 54, line 29 - page 55, line 4 page 58, line 13 - page 59, line 34 page 63, line 32 - page 68, line 1 page 69, line 7 - line 31 page 93, line 30 - page 94, line 24 page 95, line 20 - page 96, line 12	1,6,7, 9-16, 24-27, 29,31
Y	----- -/--	2,3,7,8, 17-23, 27-29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

1 October 2004

Date of mailing of the international search report

14/10/2004

Name and mailing address of the ISA

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Authorized officer

Tuynman, A

INTERNATIONAL SEARCH REPORT

International Application No

B2004/001453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RIVERA STEVEN P ET AL: "Identification of a novel dioxin-inducible cytochrome P450" MOLECULAR PHARMACOLOGY, vol. 61, no. 2, February 2002 (2002-02), pages 255-259, XP002295652 ISSN: 0026-895X cited in the application the whole document abstract	1
Y	FURUKAWA M ET AL: "Adenovirus vector-mediated reporter system for in vivo analyses of human CYP3A4 gene activation" JOURNAL OF BIOCHEMISTRY, JAPANESE BIOCHEMICAL SOCIETY, TOKYO, JP, vol. 131, no. 1, January 2002 (2002-01), pages 71-78, XP002969418 ISSN: 0021-924X the whole document in particular: abstract figures 8,9	2,3,7,8, 17-23, 27-29
A	RYLANDER TOVE ET AL: "Identification and tissue distribution of the novel human cytochrome P450 2S1 (CYP2S1)" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 281, no. 2, 23 February 2001 (2001-02-23), pages 529-535, XP002295653 ISSN: 0006-291X cited in the application the whole document	17,18, 20-26
A	DATABASE EMBL 'Online!' EBI; 23 October 2000 (2000-10-23), DOE JOINT GENOME INSTITUTE: XP002295655 retrieved from EBI Database accession no. AC011510 the whole document	2,8, 17-25, 27-29
P,X	WO 03/101376 A (COLLIN-DJANGONE CHRISTINE ; SIMONNET JEAN-THIERRY (FR); OREAL (FR); DU) 11 December 2003 (2003-12-11) claims 1-4,17-19	30-32

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INTERNATIONAL SEARCH REPORT

tional Application No

'GB2004/001453

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	SMITH G ET AL: "Cutaneous expression of cytochrome P450 CYP2S1: individuality in regulation by therapeutic agents for psoriasis and other skin diseases" LANCET THE, LANCET LIMITED. LONDON, GB, vol. 361, no. 9366, 19 April 2003 (2003-04-19), pages 1336-1343, XP004421152 ISSN: 0140-6736 the whole document -----	1-38
P, X	SMITH G ET AL: "Cytochrome P450 CYP2S1 expression in human skin: Individuality in regulation by therapeutic agents for psoriasis and other skin diseases." BRITISH JOURNAL OF DERMATOLOGY, vol. 148, no. 4, April 2003 (2003-04), page 853, XP002295654 & ANNUAL MEETING OF THE BRITISH SOCIETY FOR INVESTIGATIVE DERMATOLOGY; SOUTHAMPTON, UK; APRIL 07-09, 2003 ISSN: 0007-0963 the whole document -----	1-38

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB2004/001453

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-8, 10-16, 22, 32-38 (in part)
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-8, 10-16, 22, 32-38 are directed to a diagnostic method practised on the human/animal body or a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No

'GB2004/001453

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0179468	A	25-10-2001	AU 5532401 A	30-10-2001
			CA 2403644 A1	25-10-2001
			EP 1272638 A2	08-01-2003
			JP 2004512818 T	30-04-2004
			WO 0179468 A2	25-10-2001
<hr/>				
WO 03101376	A	11-12-2003	FR 2840217 A1	05-12-2003
			WO 03101376 A2	11-12-2003
<hr/>				

PCT

10/552610

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

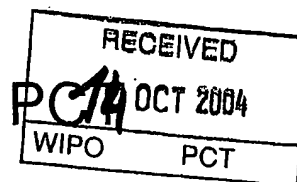
Applicant's or agent's file reference PC/JM/P13482PC	FOR FURTHER ACTION	See item 4 below
International application No. PCT/GB2004/001453	International filing date (<i>day/month/year</i>) 05 April 2004 (05.04.2004)	Priority date (<i>day/month/year</i>) 05 April 2003 (05.04.2003)
International Patent Classification (IPC) or national classification and IPC 7 C12Q 1/26, C12N 9/02, 15/00, C12Q 1/68, C07K 16/00, A61K 48/00, 38/00, C12N 5/10, G01N 33/50		
Applicant UNIVERSITY COURT OF THE UNIVERSITY OF DUNDEE		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																
2.	This REPORT consists of a total of 11 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 15%;"><input checked="" type="checkbox"/> Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. II</td> <td>Priority</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/> Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input checked="" type="checkbox"/> Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/> Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/> Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/> Box No. I	Basis of the report	<input checked="" type="checkbox"/> Box No. II	Priority	<input checked="" type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/> Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/> Box No. VI	Certain documents cited	<input type="checkbox"/> Box No. VII	Certain defects in the international application	<input type="checkbox"/> Box No. VIII	Certain observations on the international application
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<input checked="" type="checkbox"/> Box No. II	Priority																
<input checked="" type="checkbox"/> Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability																
<input type="checkbox"/> Box No. IV	Lack of unity of invention																
<input checked="" type="checkbox"/> Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement																
<input checked="" type="checkbox"/> Box No. VI	Certain documents cited																
<input type="checkbox"/> Box No. VII	Certain defects in the international application																
<input type="checkbox"/> Box No. VIII	Certain observations on the international application																
4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																

<p style="text-align: center;">The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. +41 22 740 14 35</p>	<p>Date of issuance of this report 14 October 2005 (14.10.2005)</p> <p>Authorized officer <div style="text-align: center;">Nora Lindner</div></p> <p>Telephone No. +41 22 338 89 65</p>
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/001453

International filing date (day/month/year)
05.04.2004

Priority date (day/month/year)
05.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/26, C12N9/02, C12N15/00, C12Q1/68, C07K16/00, A61K48/00, A61K38/00, C12N15/86, C12N5/10,

Applicant
UNIVERSITY COURT OF THE UNIVERSITY OF DUNDEE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-8,10-16,22,31-38 (industrial applicability), 31

because:

- ☒ the said international application, or the said claims Nos. 1-8,10-16,22,32-38 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 31 are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-8,10-16,22,32-38 (industrial applicability); 31
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-5,8,13-15,17-23,28-30,32-38
	No: Claims	1,6,7,9-12,16,24-27
Inventive step (IS)	Yes: Claims	4,5,30,32-38
	No: Claims	1-3,6-29
Industrial applicability (IA)	Yes: Claims	9,17-21,23-30
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III.

Present claim 31 relates *inter alia* to compounds or the use of such compounds defined by reference to a desirable characteristic or property, namely compounds being identified according to a method used in claims 1-17.

The claim covers all compounds having this characteristic or property, whereas the application provides neither support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claim so lacks support, and the application so lacks disclosure. To select such compounds via a method used in claims 1-17, would require undue experimentation and therefore this claim is not allowable.

Independent of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Therefore no opinion as to novelty, inventive step and industrial applicability shall given for those compounds.

Claims 1-8,10-16,22 and 32-38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

The following documents are referred to in this communication:

D1.: WO 01/79468 A (INCYTE GENOMICS INC ; PATTERSON CHANDRA (US);
TRIBOULEY CATHERINE M (U) 25 October 2001 (2001-10-25)

D2: RIVERA STEVEN P ET AL: MOLECULAR PHARMACOLOGY, vol. 61, no. 2,
February 2002 (2002-02), pages 255-259.

D3: FURUKAWA M ET AL: JOURNAL OF BIOCHEMISTRY, JAPANESE
BIOCHEMICAL SOCIETY, TOKYO, JP, vol. 131, no. 1, January 2002 (2002-01),
pages 71-78.

1 INDEPENDENT CLAIM 1

- 1.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D2 (abstract) discloses:

a method for identifying an agent capable of modulating expression of CYP2S1 by a cell, comprising the steps of :

- a) providing cells capable of expressing CYP2S1 (mouse Hepa-1 cells)
- b) contacting a test agent with said cells
- c) incubating said cells under conditions which are conducive to enable expression of CYP2S1 when in the absence of the test agent; and
- d) detecting whether or not the test agent modulates expression of CYP2S1.

Therefore, D2 anticipates claim 1.

Document D1 also discloses such a method (page 29, lines 23-27; page 69 ,lines 7-31) and suggests different cell lines to be used in such a method. (Note that SEQ ID No 6 corresponds to the amino acid sequence of CYP2S1 and SEQ ID No 16 to the corresponding polynucleotide). Therefore, D1 also anticipates claim 1.

2 INDEPENDENT CLAIM 2

- 2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 2 does not involve an inventive step in the sense of Article 33 (3) PCT.

Document D1 discloses a method for identifying an agent capable of modulating expression of CYP2S1 by a cell, from which the subject matter of claim 2 differs in that the cell comprises a promoter sequence as in Figure 7 or a fragment thereof capable of controlling transcription or translation.

The technical effect thereof is that with such a natural promoter modulators can be identified that can influence the natural expression of CYP2S1 on a different level than the coding part of the gene.

The problem to be solved is to provide non-coding gene sequences, the modulation of which will lead to an altered expression of the CYP2S1 protein.

The solution is to use a cell comprising a promoter sequence as in Figure 7 or a fragment thereof capable of controlling transcription or translation.

This solution is obvious to a person skilled in the art because the advantages of using a natural promoter are common knowledge for a person skilled in the art.

The person skilled in the art working in the field of cytochrome P450 expression systems knows for instance D3: D3 (abstract; figures 8 and 9) discloses the use of a natural promoter of CYP3A4 to identify modulators of the expression thereof.

therefore the skilled person will certainly apply this solution to arrive at a method according to claim 2.

3 INDEPENDENT CLAIM 9

- 3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 9 is not new in the sense of Article 33(2) PCT. Document D1 discloses a method for identifying an agent capable of modulating the activity of CYP2S1, comprising the steps of providing CYP2S1 (DME-6); contacting a test agent with CYP2S1 and detecting whether or not the test agent modulates the activity of CYP2S1 (D1, page 29, lines 10-22). therefore D1 anticipates claim 6.

4 INDEPENDENT CLAIMS 17-20,23

- 4.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 17-20,23 is not involving an inventive step in the sense of Article 33(3) PCT for the same reasons as under item 2. Claims 17-20 and 23 relate to the obvious constructs and methods the person skilled in the art will use to solve the problem of item 2.

5 INDEPENDENT CLAIM 24

- 5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24 is not new in the sense of Article 33(2) PCT. Document D1 discloses the protein CYP2S1 (DME-6; SEQ ID NO 6) and methods to produce this protein (page 93, line 30-page 94, line 24). There are no technical features that differentiate this CYP2S1 from a CYP2S1 produced by the method of claim 23. Therefore D1 anticipates claim 24. Even if novelty could be established, this claim would never be considered to involve an inventive step in the sense of Article 33(3) PCT, for the same reasons as mentioned under item 4.

6 INDEPENDENT CLAIM 25

- 6.1 The present application does not meet the criteria of Article 33(1) PCT, because

the subject-matter of claim 25 is not new in the sense of Article 33(2) PCT.
Document D1 discloses a pharmaceutical composition comprising CYP2S1 (page 27, line 32-page 28, line 4).

7 INDEPENDENT CLAIM 26

- 7.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 26 is not new in the sense of Article 33(2) PCT.
Document D1 discloses antibodies against CYP2S1 (page 95, line 20-page 96, line 12) and their use for measuring the expression of CYP2S1 (page 54, line 29-page 55, line 4). D1 differs from present claim 26 in that it does not explicitly state that the expression levels of CYP2S1, that are to be detected in the method mentioned under item 1.2, are to be detected via these antibodies. The problem to be solved can then be seen as the provision of a method of detecting CYP2S1 expression. The solution is to use CYP2S1 specific antibodies. This solution is of course obvious from DNA since it is common knowledge to use antibodies for detecting expression levels of a protein and D1 discloses the appropriate antibodies for this purpose (page 54, line 29-page 55, line 4).

8 INDEPENDENT CLAIM 27

- 8.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 27 is not new in the sense of Article 33(2) PCT.
Document D1 discloses the use of a recombinant vector capable of expressing CYP2S1 in gene therapy (page 63, line 32-page 68, line 1).

9 INDEPENDENT CLAIMS 30,32-38

- 9.1 The subject-matter of claim 30 is considered to be new and inventive in the sense of Article 33(2) PCT.
Document D1 discloses a list of various diseases (page 58, line 13-page 59, line 34), that may be associated with the expression of various CYPs among which CYP2S1. Although D1 mentions skin disorders in this list, there is no teaching that specifically associates CYP2S1 with skin disorders. On the contrary it can be considered a surprising effect that CYP2S1 is especially correlated with skin diseases. Therefore, all of the independent claims 30-38 that refer to the disease association of CYP2S1 with skin disorders are considered to be novel and

inventive in view of D1.

10 DEPENDENT CLAIMS 3,6-8,10-12,15,16,19, 21, 28, 29

Dependent claims 19, 21, 28, 29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

11 DEPENDENT CLAIMS 4,5,13 and 14

Dependent claims 4,5,13 and 14 meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT) for the same reasons as mentioned under item 9.

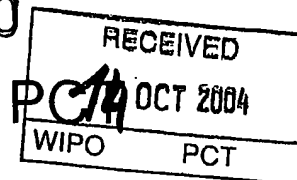
12 INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

12.1 Claims 9,17-21,23-30 are considered to be industrially applicable in the sense of Article 33(4) PCT.

12.2 For the assessment of the present claims 1-8,10-16,22 and 32-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

10/552610

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/001453

International filing date (day/month/year)
05.04.2004

Priority date (day/month/year)
05.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/26, C12N9/02, C12N15/00, C12Q1/68, C07K16/00, A61K48/00, A61K38/00, C12N15/86, C12N5/10,

Applicant
UNIVERSITY COURT OF THE UNIVERSITY OF DUNDEE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-8,10-16,22,31-38 (industrial applicability), 31

because:

- ☒ the said international application, or the said claims Nos. 1-8,10-16,22,32-38 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☒ the claims, or said claims Nos. 31 are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-8,10-16,22,32-38 (industrial applicability); 31
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/001453

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-5,8,13-15,17-23,28-30,32-38
	No: Claims	1,6,7,9-12,16,24-27
Inventive step (IS)	Yes: Claims	4,5,30,32-38
	No: Claims	1-3,6-29
Industrial applicability (IA)	Yes: Claims	9,17-21,23-30
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III.

Present claim 31 relates *inter alia* to compounds or the use of such compounds defined by reference to a desirable characteristic or property, namely compounds being identified according to a method used in claims 1-17.

The claim covers all compounds having this characteristic or property, whereas the application provides neither support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claim so lacks support, and the application so lacks disclosure. To select such compounds via a method used in claims 1-17, would require undue experimentation and therefore this claim is not allowable.

Independent of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Therefore no opinion as to novelty, inventive step and industrial applicability shall given for those compounds.

Claims 1-8,10-16,22 and 32-38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

The following documents are referred to in this communication:

- D1.: WO 01/79468 A (INCYTE GENOMICS INC ; PATTERSON CHANDRA (US); TRIBOULEY CATHERINE M (U) 25 October 2001 (2001-10-25)
- D2: RIVERA STEVEN P ET AL: MOLECULAR PHARMACOLOGY, vol. 61, no. 2, February 2002 (2002-02), pages 255-259.
- D3: FURUKAWA M ET AL: JOURNAL OF BIOCHEMISTRY, JAPANESE BIOCHEMICAL SOCIETY, TOKYO, JP, vol. 131, no. 1, January 2002 (2002-01), pages 71-78.

1 INDEPENDENT CLAIM 1

- 1.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D2 (abstract) discloses:

a method for identifying an agent capable of modulating expression of CYP2S1 by a cell, comprising the steps of :

- a) providing cells capable of expressing CYP2S1 (mouse Hepa-1 cells)
- b) contacting a test agent with said cells
- c) incubating said cells under conditions which are conducive to enable expression of CYP2S1 when in the absence of the test agent; and
- d) detecting whether or not the test agent modulates expression of CYP2S1.

Therefore, D2 anticipates claim 1.

Document D1 also discloses such a method (page 29, lines 23-27; page 69, lines 7-31) and suggests different cell lines to be used in such a method. (Note that SEQ ID No 6 corresponds to the amino acid sequence of CYP2S1 and SEQ ID No 16 to the corresponding polynucleotide). Therefore, D1 also anticipates claim 1.

2 INDEPENDENT CLAIM 2

- 2.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 2 does not involve an inventive step in the sense of Article 33 (3) PCT.

Document D1 discloses a method for identifying an agent capable of modulating expression of CYP2S1 by a cell, from which the subject matter of claim 2 differs in that the cell comprises a promoter sequence as in Figure 7 or a fragment thereof capable of controlling transcription or translation.

The technical effect thereof is that with such a natural promoter modulators can be identified that can influence the natural expression of CYP2S1 on a different level than the coding part of the gene.

The problem to be solved is to provide non-coding gene sequences, the modulation of which will lead to an altered expression of the CYP2S1 protein.

The solution is to use a cell comprising a promoter sequence as in Figure 7 or a fragment thereof capable of controlling transcription or translation.

This solution is obvious to a person skilled in the art because the advantages of using a natural promoter are common knowledge for a person skilled in the art.

The person skilled in the art working in the field of cytochrome P450 expression systems knows for instance D3: D3 (abstract; figures 8 and 9) discloses the use of a natural promoter of CYP3A4 to identify modulators of the expression thereof.

therefore the skilled person will certainly apply this solution to arrive at a method according to claim 2.

3 INDEPENDENT CLAIM 9

- 3.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 9 is not new in the sense of Article 33(2) PCT. Document D1 discloses a method for identifying an agent capable of modulating the activity of CYP2S1, comprising the steps of providing CYP2S1 (DME-6); contacting a test agent with CYP2S1 and detecting whether or not the test agent modulates the activity of CYP2S1 (D1, page 29, lines 10-22). therefore D1 anticipates claim 6.

4 INDEPENDENT CLAIMS 17-20,23

- 4.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 17-20,23 is not involving an inventive step in the sense of Article 33(3) PCT for the same reasons as under item 2. Claims 17-20 and 23 relate to the obvious constructs and methods the person skilled in the art will use to solve the problem of item 2.

5 INDEPENDENT CLAIM 24

- 5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 24 is not new in the sense of Article 33(2) PCT. Document D1 discloses the protein CYP2S1 (DME-6; SEQ ID NO 6) and methods to produce this protein (page 93, line 30-page 94, line 24). There are no technical features that differentiate this CYP2S1 from a CYP2S1 produced by the method of claim 23. Therefore D1 anticipates claim 24. Even if novelty could be established, this claim would never be considered to involve an inventive step in the sense of Article 33(3) PCT, for the same reasons as mentioned under item 4.

6 INDEPENDENT CLAIM 25

- 6.1 The present application does not meet the criteria of Article 33(1) PCT, because

the subject-matter of claim 25 is not new in the sense of Article 33(2) PCT.
Document D1 discloses a pharmaceutical composition comprising CYP2S1 (page 27, line 32-page 28, line 4).

7 INDEPENDENT CLAIM 26

- 7.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 26 is not new in the sense of Article 33(2) PCT.
Document D1 discloses antibodies against CYP2S1 (page 95, line 20-page 96, line 12) and their use for measuring the expression of CYP2S1 (page 54, line 29-page 55, line 4). D1 differs from present claim 26 in that it does not explicitly state that the expression levels of CYP2S1, that are to be detected in the method mentioned under item 1.2, are to be detected via these antibodies. The problem to be solved can then be seen as the provision of a method of detecting CYP2S1 expression. The solution is to use CYP2S1 specific antibodies. This solution is of course obvious from DNA since it is common knowledge to use antibodies for detecting expression levels of a protein and D1 discloses the appropriate antibodies for this purpose (page 54, line 29-page 55, line 4).

8 INDEPENDENT CLAIM 27

- 8.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 27 is not new in the sense of Article 33(2) PCT.
Document D1 discloses the use of a recombinant vector capable of expressing CYP2S1 in gene therapy (page 63, line 32-page 68, line 1).

9 INDEPENDENT CLAIMS 30,32-38

- 9.1 The subject-matter of claim 30 is considered to be new and inventive in the sense of Article 33(2) PCT.
Document D1 discloses a list of various diseases (page 58, line 13-page 59, line 34), that may be associated with the expression of various CYPs among which CYP2S1. Although D1 mentions skin disorders in this list, there is no teaching that specifically associates CYP2S1 with skin disorders. On the contrary it can be considered a surprising effect that CYP2S1 is especially correlated with skin diseases. Therefore, all of the independent claims 30-38 that refer to the disease association of CYP2S1 with skin disorders are considered to be novel and

inventive in view of D1.

10 DEPENDENT CLAIMS 3,6-8,10-12,15,16,19, 21, 28, 29

Dependent claims 19, 21, 28, 29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

11 DEPENDENT CLAIMS 4,5,13 and 14

Dependent claims 4,5,13 and 14 meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT) for the same reasons as mentioned under item 9.

12 INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

12.1 Claims 9,17-21,23-30 are considered to be industrially applicable in the sense of Article 33(4) PCT.

12.2 For the assessment of the present claims 1-8,10-16,22 and 32-38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.